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From Channels to Behavior: An Integrative Model of NaCl Taste

Minireview

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An issue common to sensory research is how to reconcile transduction mechanisms, elucidated by molecular and physiological studies, with perception. In gustatory research, stimuli and their transduction mechanisms are often characterized in terms of human perceptual experiences—e.g., a mechanism for citric acid–evoked depolarization of a taste receptor cell may be described as a mechanism for sour taste. Because transduction is studied in a variety of species, and because the mechanisms for common stimuli tend to vary across species, this association between transduction events at the receptor level with human perception is problematic. It is therefore important to try to relate transduction mechanisms to both neural organization and behavioral abilities of the model species. Indeed, recent studies in mammalian gustation have used a variety of techniques to construct models that link receptor mechanisms with behavioral responses. Perhaps the most complete model involves the role that the amiloride-sensitive sodium channels (ASSCs) in mammalian taste receptor cells play in determining how an animal discriminates among salt stimuli.

General Mechanisms of Taste Transduction

Taste transduction, in mammals, occurs in taste buds located in several distinct regions on the tongue, palate, and other areas of the oral cavity. Sapid stimuli interact with receptors or ion channels on the apical membranes of taste receptor cells (TRCs), producing a depolarization, or receptor potential, within the cell. The receptor potential ultimately results in a rise in intracellular Ca^{2+} that triggers transmitter release onto the gustatory nerve fibers (Figure 1). These fibers from the VIIth, IXth, and Xth cranial nerves converge on second-order brainstem gustatory neurons in the nucleus of the solitary tract (NST).

Although a family of taste receptors has not yet been cloned, recent studies have indicated that G protein–coupled receptors are involved in the transduction of stimuli characterized by humans as sweet or bitter tasting (Wong et al., 1996; additional references regarding transduction can be found in Lindemann, 1996, and Gilbertson, 1998a). The G proteins gustducin and transducin, which are expressed in a subset of TRCs, are activated when bovine taste membranes are stimulated by bitter-tasting compounds such as denatonium and strychnine, indicating the presence of membrane-bound receptors (Ming et al., 1998). Activated gustducin (and/or transducin), in turn, causes an increase in phosphodiesterase activity, resulting in decreased levels of cAMP, ultimately leading to an increase in Ca^{2+} influx. In addition, sugars and artificial sweeteners apparently activate G protein–coupled receptors. The transduction pathway for sugars involves the G protein–mediated activation of adenylyl cyclase and the production of cAMP, whereas saccharin, an artificial sweetener, activates phospholipase C, causing the production of IP_3 (Cummings et al., 1996). Either pathway ultimately results in a block of voltage-gated K^+ channels in TRCs leading to depolarization, but this does not necessarily imply the existence of multiple sweet taste mechanisms within a single cell.

Other receptor-mediated events have been implicated in the transduction of taste stimuli in mammals. The receptor for glutamate taste ("umami") may be a metabotropic glutamate receptor that has been cloned from rat taste cells (Chaudhari et al., 1996). Additionally, recent studies in rat indicate the existence of a taste transduction mechanism for dietary fat: essential fatty acids, generated by the actions of lingual lipase on fats, directly

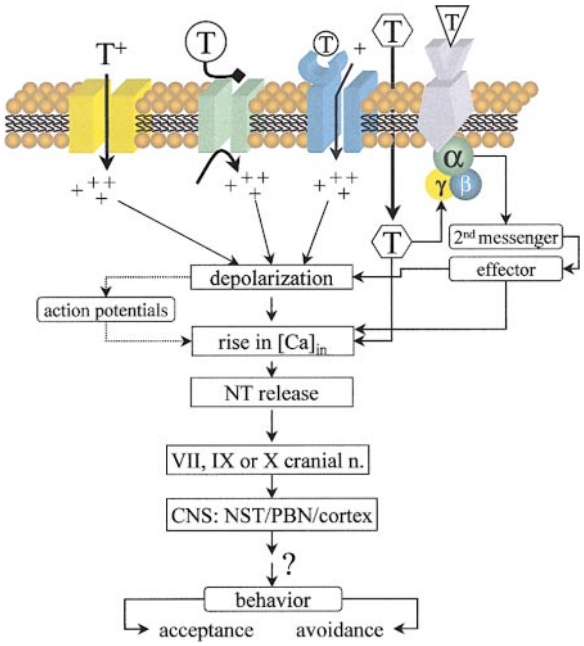

Figure 1. General Taste Transduction Pathway

Taste stimuli (T) are transduced by a variety of receptive mechanisms in taste cells, including (from left to right) permeation of ion channels, inhibition of ion channels, activation of ionotropic receptors, direct permeation of the plasma membrane, and activation of metabotropic receptors (see text and Lindemann, 1996). Typically this leads to a depolarization of the receptor cell, generation of action potentials, and a rise in intracellular Ca^{2+}, which is the common endpoint for all taste stimuli. Release of the taste cell neurotransmitter (NT) activates afferent nerve fibers (cranial nerves VII, IX, or X). This information is carried to the nucleus of the solitary tract (NST), parabrachial nucleus (PBN), and gustatory cortex and is ultimately used by the organism to make judgements about the acceptability of the tastant.

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inhibit delayed rectifying K^+ channels in TRCs (Gilbertson et al., 1997), leading to depolarization. Thus, it has been suggested that a putative "receptor" for fatty acids may be the Shaker Kv1.5 channel in TRCs (Liu et al., 1998).

Ionic taste stimuli such as salts and acids exert their effects on TRCs by direct interactions with ion channels. Amiloride is a diuretic that is known to specifically block some epithelial Na^+ channels and produce gustatory effects. Na^+ permeates amiloride-sensitive sodium channels (ASSCs) on the apical surface of TRCs (see below), but NaCl also evokes a response in TRCs that do not possess functional ASSCs. The nature of this other salt mechanism is not yet completely understood but may have to do with the ability of cations to diffuse through tight junctions between TRCs in an anion-dependent fashion (Ye et al., 1991). Protons also penetrate ASSCs, the same channels involved in sodium salt transduction (Gilbertson et al., 1993), and lingual amiloride blocks acid-evoked responses in a subset of nerve fibers and second-order gustatory neurons (Boughter and Smith, 1998). Recently, Ugawa et al. (1998) localized a type of proton-gated cation channel, similar to mammalian degenerin-1 (MDEG1), in taste buds of the rat. Application of acid elicits large inward currents in oocytes expressing MDEG1. The MDEG1-mediated conductance is also amiloride sensitive and may account in part for the amiloride-sensitive acid response.

A Model of Salt Taste Discrimination

Though a fair amount is known about the transduction of individual tastants, there is scant evidence linking these specific transduction mechanisms with stimulus-evoked behavioral responses such as discrimination or rejection. The one exception to this involves the role of ASSCs in the transduction of sodium salts (and acids), which has been investigated in rats and hamsters at all levels along the gustatory pathway from receptor cell to behavior. The results of these various studies confirm that a significant portion of NaCl taste is mediated via an influx of sodium ions through ASSCs (references can be found in Lindemann, 1996).

Electrophysiological studies of the permeability properties of ASSCs in mammalian taste cells reveal that these channels are significantly permeable to Na^+, Li^+ and H^+, have single channel conductances of $\sim$5 pS, and are blocked by submicromolar concentrations of amiloride. Based on these properties, it has become increasingly clear that the ASSCs in taste cells are similar molecularly and functionally to the heterooligomeric epithelial sodium channels (ENaCs) found in a variety of sodium-transporting epithelia. Recent RT–PCR and immunocytochemical studies confirm the presence of ENaC subunits in rat TRCs (e.g., Lindemann et al., 1998). Similar to their epithelial counterparts, the activity of ASSCs in TRCs is regulated by a number of natriferic hormones, hormones that control Na^+ transport (Gilbertson, 1998b).

Recent studies using amiloride to inhibit physiological and behavioral responses to sodium salts have provided a basis for a model of sodium salt taste linking the ASSC transduction mechanism to taste-guided behavior in mammals. Single gustatory nerve fibers and their primary target neurons in the NST are, as a rule, rather broadly responsive to stimuli of different taste qualities. However, a subset of individual fibers and neurons can be classified as "Na^+-best" because they have a strong response to sodium and lithium salts relative to other stimuli. Others respond to sodium salts, but, importantly, they also respond well or better to nonsodium salts and acids. It was appreciated in early taste research that activity in different fiber types may contribute to a neural code for taste discrimination (Pfaffmann, 1959).

The effects of lingual amiloride on taste responses in different neuron types of the NST, whose second-order gustatory neurons are a potential substrate for taste discrimination and other taste processes, have been studied in rats (Scott and Giza, 1990) and hamsters (Boughter and Smith, 1998). In both species, responses to NaCl in Na^+-best neurons were significantly reduced or eliminated by micromolar concentrations of amiloride. Responses to NaCl in those cells broadly responsive to both salts and acids were completely unaffected. Although there is convergence of peripheral fibers onto gustatory neurons in the NST, input from different receptor mechanisms ultimately activates separate populations of neurons.

In order to understand how the activity of afferent fibers and CNS neurons that are sensitive to amiloride may provide a basis for taste discrimination, Spector and colleagues tested the ability of amiloride to disrupt the discrimination between NaCl and KCl (Spector et al., 1996). They conducted elegant behavioral experiments in the rat using an operant conditioning paradigm in which water-restricted rats were trained to discriminate between two different taste stimuli, NaCl and a nonsodium salt (KCl). Because there were both positive and negative consequences of each identification (i.e., presence or absence of water reward), the rats were more likely to report subtle differences between taste stimuli than in standard two-bottle preference tests. When the amiloride, which itself is tasteless to rats, was added to the salts, rats trained to distinguish between the two salts could no longer make the discrimination, performing at a level no better than chance. The effect of amiloride was significant at 10 μM, a concentration effective in receptor cell physiology experiments. The pattern of behavioral responses suggested that amiloride predominantly affected the taste quality of NaCl rather than KCl, which is consistent with electrophysiological observations that KCl does not elicit a strong response in the amiloride-sensitive Na^+-best cells (Scott and Giza, 1990). After amiloride treatment, the information contained in the neural pattern of activity is insufficient to discriminate sodium from a nonsodium salt. Despite the fact that the distribution of ASSC inputs to NST neurons is specific, the physiological data may, in fact, argue against a particular neuron type functioning as a "labeled line" for sodium salts. Na^+-best neurons respond to multiple stimuli, and both NaCl and acid responses were blocked by amiloride in these cells in the hamster NST (Boughter and Smith, 1998). This organization suggests that any one neuron type alone or any one transduction mechanism alone may be insufficient for the discrimination among different-tasting stimuli.

As more taste transduction mechanisms are elucidated, it will be necessary to attempt to link the effects

of tastants at the receptor cell level with, ultimately, the behavior of the organism. For example, bitter taste in humans is stimulated by a diverse array of compounds, ranging from simple salts to toxic plant alkaloids. Multiple transduction mechanisms for bitter stimuli have been proposed (e.g., Gilbertson, 1998a). But behavioral studies with rodents indicate that while many of these compounds provoke an avoidance response, others do not. To understand how the mammalian CNS encodes bitter and other taste qualities will require the integration of research at the receptor cell, afferent nerve fiber, central taste nuclei, and behavioral levels.

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